Non-convulsive status epilepticus

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Abstract

The clinical, electrographic and reported neuropsychological features of 50 children with non-convulsive status epilepticus (NCSE) were reviewed and the children's progress followed for one to five years. NCSE occurred in a variety of epilepsies, especially the Lennox-Gastaut syndrome. Clinical manifestations ranged from obvious mental deterioration to subtle changes. The condition had often been overlooked or misinterpreted and many children had experienced repeated episodes over long periods. Following diagnosis, immediate treatment was often not attempted or was not successful. Further episodes of NCSE occurred in the majority of children during the follow up period. Failure to recognise NCSE and to treat episodes promptly, and the high rate of recurrence, is of particular concern in view of fears that repeated exposure to this condition might be brain damaging. At least 28 children in the present series showed evidence of intellectual or educational deterioration over the period during which NCSE had occurred, although the exact cause was difficult to determine.

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Non-convulsive status epilepticus (NCSE) usually consists of a prolonged seizure state predominantly affecting mental function. This condition is not rare and is likely to be encountered in paediatric practice, especially in disabled children with epilepsy. It is often misdiagnosed or undiagnosed and, even when recognised, may not be treated with any urgency.¹

Publications on NCSE are scattered and largely consist of reports of single cases or small series. From these accounts and reviews^{1–3} certain important issues of practical and theoretical importance can be identified. These include the complexities of classification (especially in children), the wide range of clinical manifestations of NCSE, the uncertainties of immediate and long term treatment, and the possibility that prolonged exposure to seizure discharge (whether accompanied by prominent clinical manifestations or not) can cause brain damage and intellectual decline. Clearly, more systematic investigation of this important and intriguing form of epilepsy is required but in the meantime what is already known needs to be more widely disseminated.

The present study consists of a mainly retrospective review of a large group of children in whom a diagnosis of NCSE was made when first seen in a children's epilepsy and EEG service. The analysis of the findings places special emphasis on the type of epilepsy or epilepsy syndrome in which these forms of status had arisen, the relationship between electrographic features and clinical manifestations, the difficulties of recognition that can arise, medical treatment given, and the course of the disorder.

Methods

SUBJECTS

Over a 12 year period 50 children referred to the epilepsy service or the Oxford regional paediatric EEG service at the Park Hospital in Oxford were considered to be in NCSE following EEG investigation. The children had been referred to these services for investigation of changes in behaviour, poor school progress, unsatisfactory seizure control, or for general review. The diagnosis of NCSE was made when prolonged periods of seizure activity in the awake state appeared to have an effect on the child's mental state in the absence of obvious motor manifestations. In addition to this series of 50 children, two others were identified over the same period as having electrical status epilepticus during slow wave sleep (ESES).⁴ These have not been included in the present account which is concerned with the direct association between sustained seizure activity during the awake state and psychological function. Children with hypsarrhythmia (considered by some to be a form of NCSE) and babies under the age of 2 years were also not included in this series on the grounds that both of these groups present special problems in assessing electroclinical correlations.

PROCEDURE AND ASSESSMENTS

EEG

In most cases the condition was diagnosed initially by means of standard EEG recordings which revealed continuous or nearly continuous seizure discharge, usually generalised in distribution, without obvious motor accompaniments of a convulsive type. In these cases EEG recordings were repeated as indicated to assess the relationship between EEG and clinical features. In 10 children prolonged recordings by means of ambulatory EEG monitoring,⁵ or combined EEG and video procedures, were necessary to confirm the clinical suspicion that NCSE was occurring intermittently, usually in subtle form, or to assess the electroclinical associations in more detail.

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Psychological development

The past clinical notes of all the children in the series were obtained and scrutinised for recorded details of early and later developmental progress, and past psychological changes that seemed likely to have marked the onset and subsequent recurrence of each child's NCSE. This information was supplemented by information obtained by writing to parents, schools, and psychological services for successive records. These were examined with special emphasis on the child's abilities or behaviour before or soon after the onset of NCSE and subsequently, including the most recent changes prior to the investigation by the Park Hospital services.

Psychological assessment

Psychological assessment at the time that NCSE was diagnosed at the Park Hospital consisted principally of general observations by staff. In six of the children who underwent special monitoring, a standardised protocol was used consisting of orientation assessment and tests of short term memory, delayed recall, perceptual speed, copying, and visuomotor skills. These assessments were repeated when the child was no longer in status.

Medical details

Medical details concerning the general nature and cause of each child's epilepsy, and any special investigations, were recorded from past clinical notes.

Follow up information

Follow up information was collected from parents, schools, physicians, and psychologists over a period of one to five years after the child was first assessed at the Park Hospital. This information covered the more recent course of the child's epilepsy, including further episodes of status, and psychological development.

Results

GENERAL

The 50 children ranged in age from 2 to 15 years at the time of referral to the Park Hospital services. Thirty two were boys. Age at onset of the seizures varied from infancy to 10 years.

Retrospective inquiries suggested that the duration of the current episode of NCSE at the time it was diagnosed at the Park Hospital had varied widely from a few hours to a few days (five cases), to several days to a few weeks (30 cases) or even longer (up to several months) in the rest. Twenty children were judged to have had previous episodes of NCSE before their assessment at the Park Hospital. This was inferred largely from parent and teacher records indicating periods of mental deterioration of generally uncertain cause, although EEG confirmation was available in a few cases. The period over which these episodes had occurred ranged from three months to six years

in 17 children; it was difficult to judge the duration of exposure to NCSE in the other three. In all but one child the diagnosis of epilepsy had preceded the first episode of non-convulsive status.

UNDERLYING EPILEPSIES

Table 1 shows the various types of epilepsy syndrome⁶ associated with NCSE in the present series. Eighteen children were classified as having the Lennox-Gastaut syndrome on the grounds that they had a variety of seizure types (especially tonic, clonic, and atypical absences) starting in early childhood and associated with developmental delay, plus slow background EEG rhythms, multifocal abnormalities, and slow (less than 3 Hz) spike wave discharges. Thirteen children corresponded to the picture of epilepsy with myoclonic-astatic seizures, that is, early onset usually with normal initial development, various seizure types (including those included in the name of the condition), and irregular fast spike or polyspike wave discharge with somewhat slow background rhythms. During NCSE the EEG in both these subgroups contained widespread irregular 4-7 Hz spike wave activity with a variable proportion of spike to waves from one child to another and from one time to another in the individual case. Children in these two subgroups could be described as having 'atypical absence status'.

Three children had childhood absence epilepsy with classical, regular, well organised 3 Hz spike wave discharge during NCSE ('typical absence status'). Twelve had partial epilepsies: six had predominantly simple partial seizures and the other six had complex partial seizures. Sometimes secondary generalisation occurred in both these subgroups. In these partial cases the EEG abnormality during NCSE consisted of widespread slowing with bilateral, or occasionally unilateral, irregular spike wave or sharp wave discharges with inconsistent localisation. In view of the partial nature of these children's epilepsies and the impairment of consciousness during their periods of NCSE, their NCSE was considered to be complex partial, mixed, or transitional in type. Four children had seizure disorders which were difficult to classify. They had a mixture of seizure types but no other characteristic clinical or EEG features. During NCSE, their EEGs contained slow background rhythms and generalised spike wave discharges at frequencies about 3 Hz.

Table 2 indicates the intellectual levels assessed during the course of the children's epilepsy. The majority of the children in the

Table 1 Non-convulsive status epilepticus: subgroups according to type of epilepsy

Type of epilepsy	No	Male	Female
Lennox-Gastaut syndrome	18	11	7
Epilepsy with myoclonic-astatic seizures	13	12	1
Childhood absence epilepsy	3	1	2
Partial epilepsy	12	3	9
Unclassifiable	4	4	0
Totals	50	31	19

Table 2 Intellectual levels of children with different types of epilepsy

Type of epilepsy	No	Severe learning disability	Moderate to mild learning disability	Average ability
Lennox-Gastaut syndrome	18	16	2	0
Epilepsy with myoclonic-astatic seizures	13	2	6	5
Childhood absence epilepsy	3	0	0	3
Partial epilepsy	12	3	2	7
Unclassifiable	4	1	0	3
Totals	50	22	10	18

series showed some degree of learning disability, often severe. However, this applied overwhelmingly to the Lennox-Gastaut subgroup with many children in the other subgroups displaying levels of intelligence within the normal range.

ELECTROCLINICAL ASSOCIATIONS

The clinical picture of children in NCSE, as judged by direct observation at the Park Hospital as well as by past descriptions in some cases, varied widely. The change in behaviour was considered obvious in 32 cases in that the duration of the episode was associated with clear and sustained alteration. This consisted essentially of a reduction of activity, slowness, and impairment of consciousness to varying degrees constituting a confusional state or even semistupor ('pseudodementia'). Poor balance or incoordination ('pseudoataxia'), usually associated with intermittent bilateral jerks of the limbs, was reported as an additional prominent feature in eight of this group. Table 3 lists some descriptions by parents, teachers, or hospital staff of children during NCSE and on remission. The first group of descriptions refer to changes in awareness and responsiveness; the second group to coordination problems. These items show a range of behavioural changes, but all are readily recognisable. In another 14 children the change was much more subtle, such as mild clouding of consciousness, even in the presence of gross EEG abnormality including generalised, regular, well organised 3 Hz spike wave in one of the cases of typical absence status. Relationships between electrographic and clinical features were difficult to discern in the remaining children because of the severity of their basic intellectual disability.

RECOGNITION

In only 20 of the 50 children was the diagnosis

Table 3 Non-convulsive status epilepticus: examples of psychological features as described by observers

During NCSE	On remission
'forgetful'	'brighter'
'difficult to motivate'	'more alert'
'excessively sleepy'	'more talkative'
'lost and disorientated'	'happier'
'unresponsive'	'like a fog was lifted from her mind'
'switches off'	
'zombie-like'	
'apparently deaf and blind'	
'drugged state'	
'poor balance'	
'frequent falls'	
'poor control of movements'	

of NCSE considered by the physician when referring the child to the epilepsy or EEG service. In these cases an EEG was requested to confirm the diagnosis. In the majority, the reason for referral was usually an open ended inquiry into the reason for the child's deteriorated behaviour or poor school progress, with mention in some cases of such possible explanations as antiepileptic drug intoxication, progressive cerebral pathology, or psychological disorder. One child had previously been referred to a child psychiatrist because her early morning slowness and reluctance to get ready for school were interpreted as school refusal. Prolonged EEG recordings showed that she was frequently in complex partial status in the mornings. Only when video/EEG recordings with simultaneous psychological test results were shown to the teachers of another child, were they convinced that her intermittent moodiness and relative unresponsiveness were manifestations of her epilepsy.

PRECIPITATING FACTORS

There was substantial evidence of a specific factor immediately preceding the onset of a period of NCSE in only four cases in this series. In one child this was the onset of a febrile illness, and in the other three cases abrupt withdrawal of antiepileptic medication seemed to have precipitated the episode.

TREATMENT

Following their EEG recording indicating NCSE, the children referred from other hospitals to the EEG service were returned to the care of their local paediatric services. Only 25 of the total series received immediate treatment for the condition. This consisted of intravenous or rectal diazepam. Prompt suppression of the seizure activity was achieved in 17 children, with clinical improvement noted after the sedative effects of the treatment had worn off, although this response lasted only a matter of hours in eight. In the remaining eight no EEG or clinical improvement was apparently achieved. Response to treatment did not seem to vary much from one type of epilepsy to another (table 4). Adjustments in the child's continuous medication, in an attempt to suppress further episodes of NCSE, were made in only 26 of the series.

FOLLOW UP

By the time of follow up (maximum five years), seizures had ceased to occur for at least 12 months in 20 children. Up to the point of remission in these children, or to the time of the follow up in the remainder, further episodes of NCSE had continued to occur after diagnosis at the Park Hospital in 37 of the 50 children.

All but four of the total series were still taking antiepileptic medication, including two children who had undergone surgery for their partial seizure disorder. Those children who had suffered further episodes of NCSE were

Table 4 Response to immediate treatment for non-convulsive status epilepticus in relation to underlying epilepsy

Type of epilepsy	No	Sustained response	Brief response only	No response
Lennox-Gastaut syndrome	9	2	4	3
Epilepsy with myoclonic-astatic seizures	8	3	3	2
Partial epilepsy	8	4	1	3
Totals	25	9	8	8

not characterised by any particular underlying epilepsy. The adjustments made to continuous medication following diagnosis of NCSE, in an attempt to prevent further episodes, were variable in nature. This, as well as the complicated treatment regimens (with multiple drugs, and ketogenic diet in 12 cases) and the limitations in the available information for the follow up period, made generalisations about the effectiveness of these changes of treatment impossible. In the 26 cases where such adjustments were made, the most consistent change associated with non-recurrence of NCSE was an increase in the dosage of sodium valproate (seven cases) or the addition of ethosuximide to sodium valproate (four cases). There was no obvious example of NCSE being precipitated by any particular antiepileptic drug.

As far as possible, comparisons were made between (a) each child's level of intellectual or educational function before NCSE had developed (or soon after its first occurrence) and (b) the level at the time of follow up or, in the 20 cases where the epilepsy had remitted, before this improvement had occurred. Twenty seven of the 50 children showed convincing evidence of intellectual or educational deterioration over this period. In the remaining 23 sufficient information was not available to allow the course of their cognitive development to be assessed reliably. Table 5 shows this deterioration in relation to underlying types of epilepsy.

An attempt was then made to judge the educational or intellectual development during the period of remission of the 20 children whose seizures, including episodes of NCSE, had apparently ceased. Five appeared to have made a significant improvement but the rest, although often considered by their parents or teachers to be more alert, were still functioning at the same intellectual level as before remission of their seizures.

Discussion

This study involved the largest published series of children with NCSE known to the authors. However, it is subject to limitations imposed by its partly retrospective nature and its

reliance on clinical information not compiled specifically for the purpose of the investigation. Even so, the findings raise a number of issues and general principles which deserve more clinical and research attention.

NCSE was found to complicate a wide variety of the childhood epilepsies, sometimes from a very early age, often repeatedly and for long periods. Its clinical presentation ranged from dramatic to very subtle effects on mental function but, even in its more clinically obvious form, it was commonly not considered as the cause of mental deterioration. Immediate treatment of the condition was often not provided and the recurrence rate was high. Many children deteriorated intellectually during the course of their exposure to NCSE.

Terminology and classifications are themselves problems.¹ NCSE is a very broad term which applies to any prolonged seizure of a non-convulsive type. Although most emphasis is placed on absence status (and to a less extent on complex partial status), patients have been described whose status has consisted of prolonged expressions of the many other types of generalised and partial non-convulsive seizures. For the present series, classification into absence status (typical or atypical) and complex partial status seemed to be sufficient for those cases where clinical accompaniments of the prolonged seizure activity could be identified. Earlier terms such as 'minor epileptic status'⁷ were avoided because of their imprecision.

The prevalence of NCSE is unknown and likely to remain so until the condition is better recognised. On the evidence of the present study, it can be expected to occur in any main category of epilepsy, both generalised and partial. The most usually reported form (absence status) is generally thought to occur mainly in patients with the Lennox-Gastaut syndrome, although children with the less common myoclonic-astatic epilepsy are said to be particularly prone.² The present findings are in keeping with such reports as 60% of the series came from within these two categories of seizure disorder. The results also indicate that childhood NCSE almost always complicates a pre-existing epilepsy.

Relatively few cases in the present series were suspected to be NCSE on referral to the Park Hospital series. There are probably two main reasons for this: (1) the relatively non-specific nature of the mental changes often seen and lack of familiarity with NCSE as a possible explanation for such changes, and (2) the subtlety of the clinical manifestations in some cases, as mentioned earlier.

In cases where the behavioural changes were prominent, reduction in activity and mental processing seemed to be equally a feature of the examples of generalised, complex partial, and mixed or transitional types of NCSE. Although more florid manifestations might be expected in seizures of temporal lobe origin, these were not convincingly recorded. This is in keeping with the evidence from published reports that there is no clear cut separation in the clinical symptomatology of

Table 5 Evidence of mental deterioration from onset of non-convulsive status epilepticus to follow up in relation to underlying type of epilepsy

Type of epilepsy	No	Evidence of deterioration	Uncertain
Lennox-Gastaut syndrome	18	7	11
Epilepsy with myoclonic-astatic epilepsy	13	7	6
Childhood absence epilepsy	3	0	3
Partial epilepsy	12	11	1
Unclassifiable	4	2	2
Totals	50	27	23

the different types of NCSE, at least in children.¹

Fluctuation of awareness, which has been claimed to be a useful diagnostic sign of NCSE, was often noted in the present series. Cyclical alternation between complete unresponsiveness – speech arrest and stereotyped automatisms (associated with temporal lobe discharges) and partial responsiveness – partial speech and apparently purposeful automatisms (associated with bilateral slow activity and low voltage fast activity in the EEG) – is said to be a feature of complex partial status in adults.⁸ This was observed in only two children in this series.

There seems to be nothing specific in these obvious psychological manifestations of NCSE although the presence of myoclonic jerks, either seen or detected on palpation, is strongly suggestive of the condition. That being so, as in this series explanations for the mental changes other than NCSE may be entertained. These include organic factors, for example overdosage with antiepileptic drugs, postictal states, or progressive cerebral pathology. Alternatively, a primarily psychiatric diagnosis is made such as depression, hysteria, or psychosis.

The subtle mental changes sometimes associated with even gross EEG abnormality can constitute a major obstacle to correct diagnosis. This curious dissociation illustrates that, although related to each other to some degree, the clinical and electrographic phenomena depend on different systems. In this series the factors generally predictive of obvious clinical effect of the seizure discharge were male sex, learning disability before the onset of the seizure disorder, and generalised seizure discharge. It is in the more subtle forms of NCSE that the use of prolonged EEG monitoring, especially by means of ambulatory cassette recordings combined with good clinical observations, can be particularly helpful in children where this condition is suspected.

Clear cut precipitants of NCSE seemed very few in this series. They may well have been underestimated by failure to inquire about them at the time or by inadequately accurate recall of past events and circumstances. A wide range of possibilities exists, including intercurrent illness, withdrawal of medication, or emotional factors, which might be particularly difficult to identify retrospectively because of informants' own involvement in the situation. It is, however, accepted that NCSE may occur without any specific precipitating factor.

Both immediate and prophylactic treatment predictably posed problems in the present group of children. First, in only about half the children was any attempt made to terminate the episode of NCSE once it had been diagnosed. This approach, which contrasts markedly with that towards convulsive status epilepticus, presumably arises from the belief that the episode will resolve spontaneously and no particular harm will be done in the meantime. The first of these assumptions is correct although, as has already been described, the episode may last for a long while, and during

this period the child's general wellbeing is compromised. Unfortunately, where NCSE is treated with some degree of urgency, the results can be disappointing even when a range of treatments are attempted in turn.^{9 10}

Prevention of the recurrence of NCSE by adjustments to continuous medication can be similarly difficult. Although there seemed to be a trend in the present series for the use of sodium valproate in particular to be associated with non-recurrence of NCSE (in keeping with reports from other sources¹¹), the majority of the children continued to have further bouts of NCSE in the follow up period. The general impression gained is that poor prognosis applies mainly to patients with generalised brain damage although in the present series, as in other reports, it was difficult to judge the thoroughness with which prevention of further NCSE episodes had been attempted. More convincing therapeutic effects may emerge in the future with the use of newer antiepileptic drugs.

The frequent failure to recognise episodes of NCSE at an early stage, the apparent length of some of the episodes, and the common absence of prompt treatment or inability to prevent further occurrences are all particularly worrying features in the present series, in view of the concern that has been expressed for some time by a number of authors that prolonged exposure to NCSE may cause dementia.^{7 12-14} Some support is lent to this fear by experimental studies which seem to implicate prolonged seizure discharge per se in neuronal damage.¹⁵ This matter is far from resolved but it is noteworthy how often children in this present series showed definite or intellectual decline over the course of a seizure disorder of which periods of NCSE had been a part. The information available in this study does not permit any accurate analysis of the nature of such deterioration, or the ways in which it might have come about.

Detailed prospective studies, with systematic documentation of cases including neuropsychological assessment, are clearly required to settle these important issues. In particular, there is need to clarify the relative contributions to intellectual decline (and other behavioural changes) of NCSE, the underlying condition of which the epilepsy is a part, and other aspects of the seizure disorder and its treatment. In the meantime, however, it is important to improve the recognition of NCSE and treat it more vigorously than is usually the case. NCSE should be particularly suspected in children with epilepsy who undergo an otherwise inexplicable change of behaviour. EEG studies will usually be helpful, especially if the results can be compared with those obtained before the change of behaviour. Treatment should involve attempts to terminate the episode and to prevent recurrences. Monitoring of the child's behaviour by means of parents' and teachers' observations should aid early detection of further episodes.

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